Effectiveness vs. Efficacy

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Will the Sun Rise Tomorrow?

Yes = 300

No = 0

chi sq = 150

p = .0001

Will the Sun Rise Tomorrow?

Yes = 10

No = 0

Chi sq = 5.0

p = 0.05

Do You Like Chocolate or Vanilla Ice Cream?

Chocolate = 100

Vanilla = 200

chi sq = 17.14

p = .003

In Hershey, Pennsylvania: Do You Like Chocolate or Vanilla Ice Cream?

Chocolate = 250

Vanilla = 50

chi sq = 75.0

p = .0001

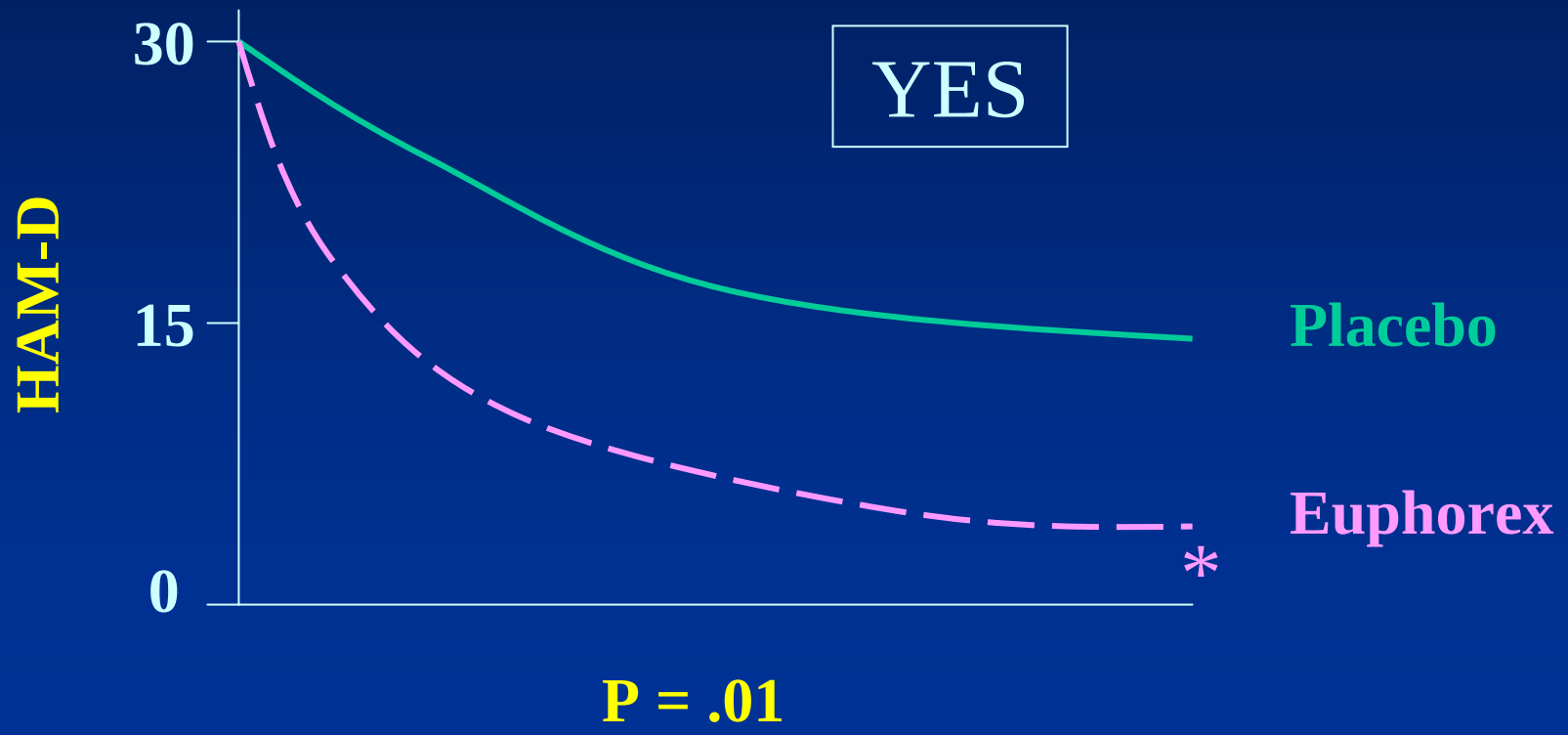
The “p” Value Only Tells Us the Likelihood (probability) that Our Observation is More than Chance

It gets bigger with

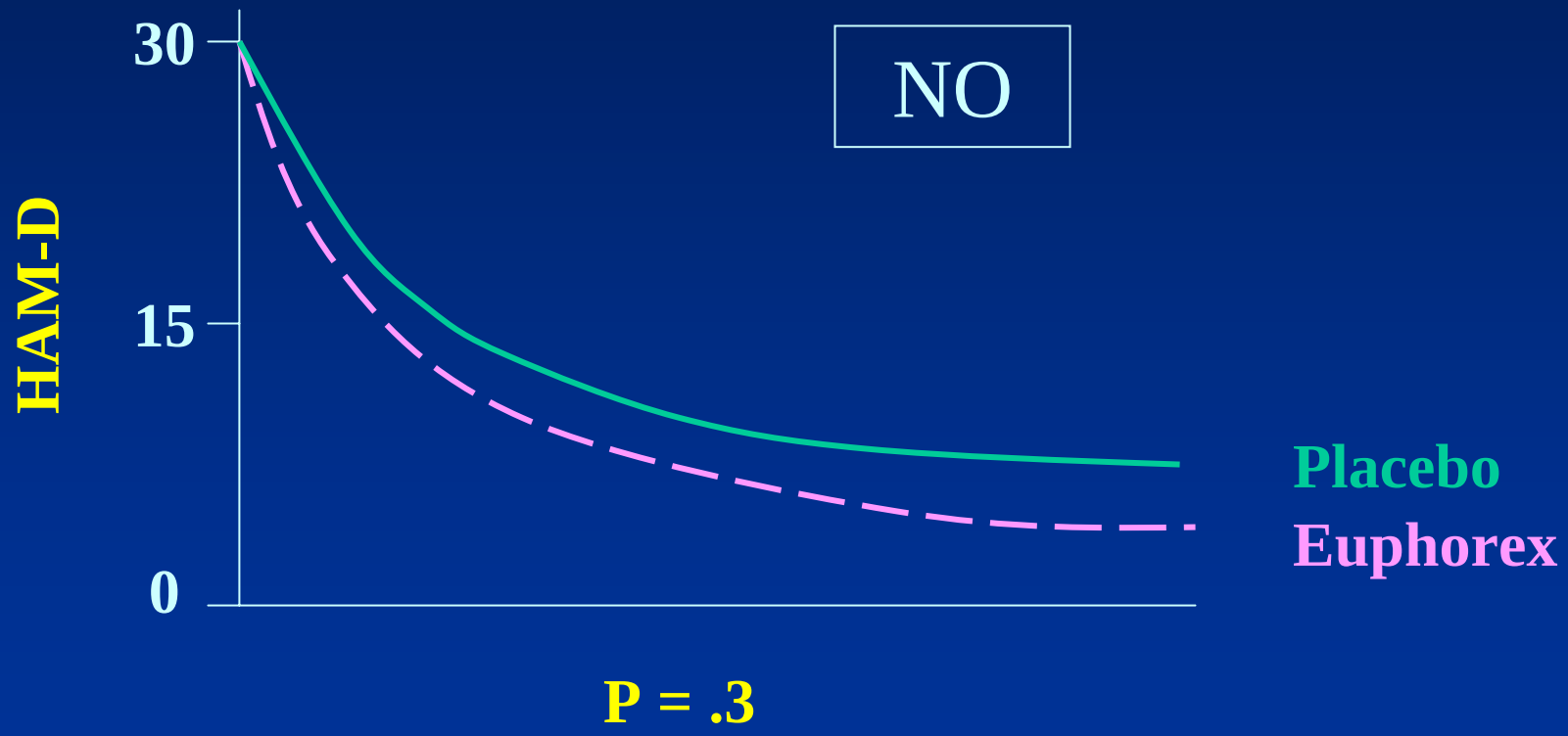
⬆ Sample Size

⬇ Variance

Is a New Antidepressant More Effective than Placebo?



Is the Same New Antidepressant More Effective than Placebo?



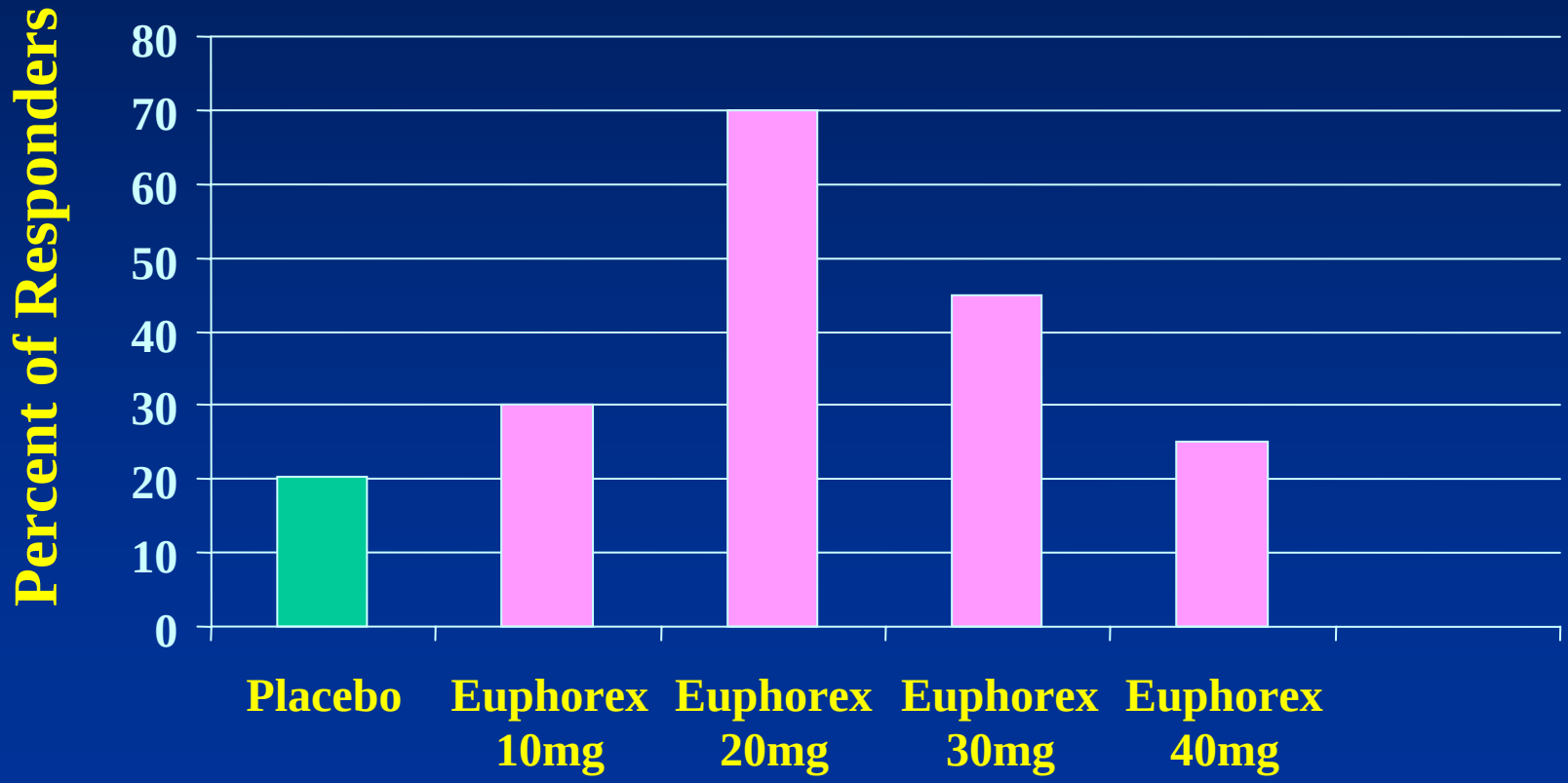
The Message: About 50% of Placebo-Controlled Studies Fail Because of High Placebo Response Rate

Placebo response goes up with

- ⇩ Severity of baseline illness
- Occult drug use
- Professional research subjects
- Small samples per site

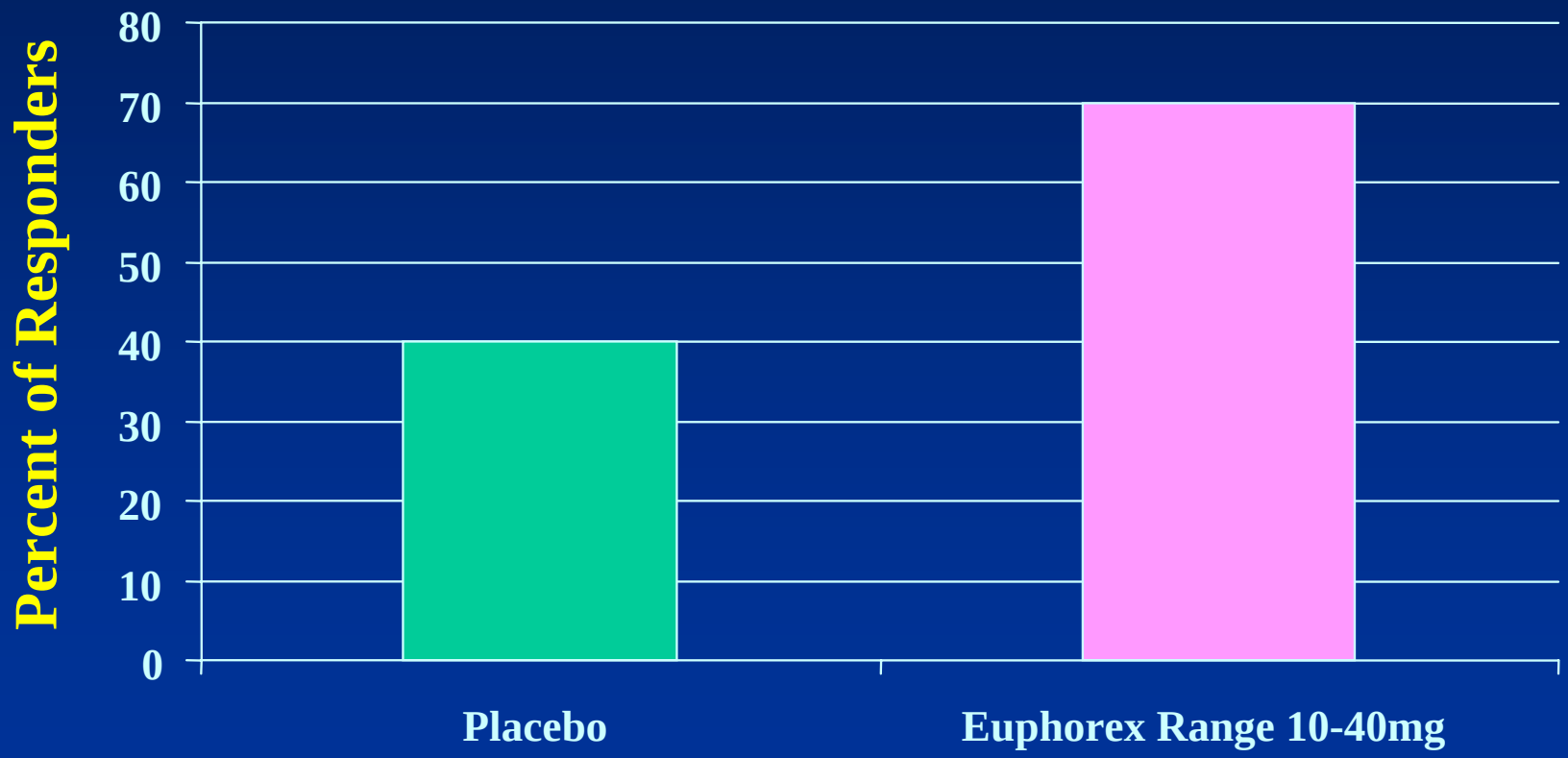
What is the Right Dose of a New Antidepressant?

Dose-ranging Study



What is the Right Dose of a New Antidepressant?

Flexible Dose Study

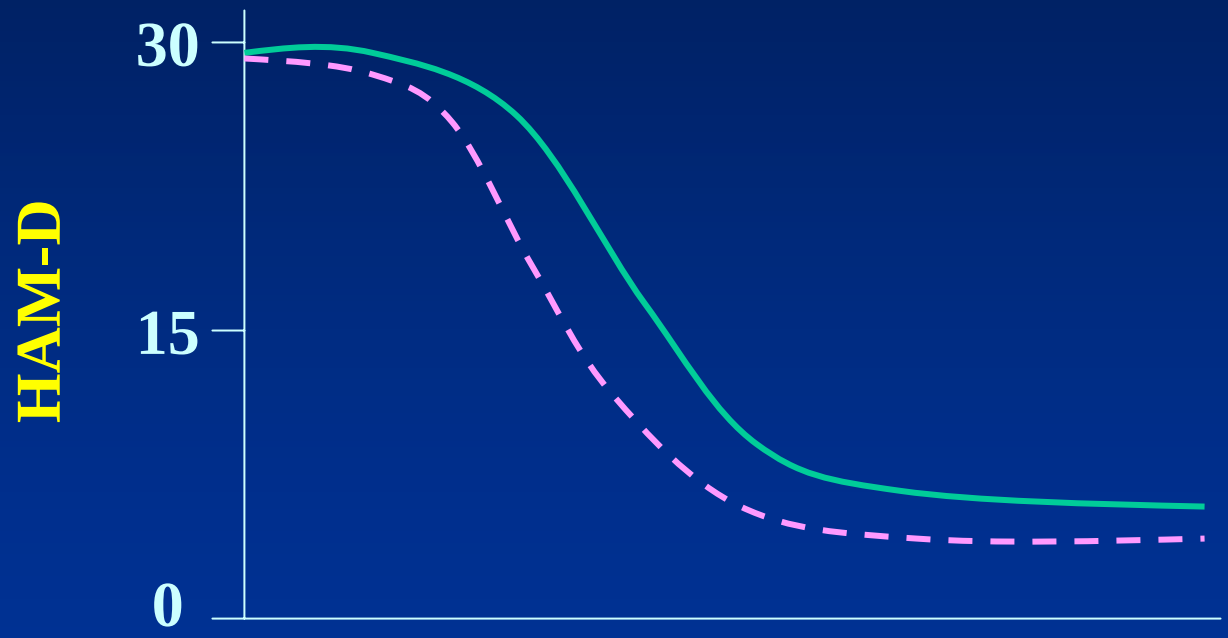


Dose Finding Should be Done as Early as Possible

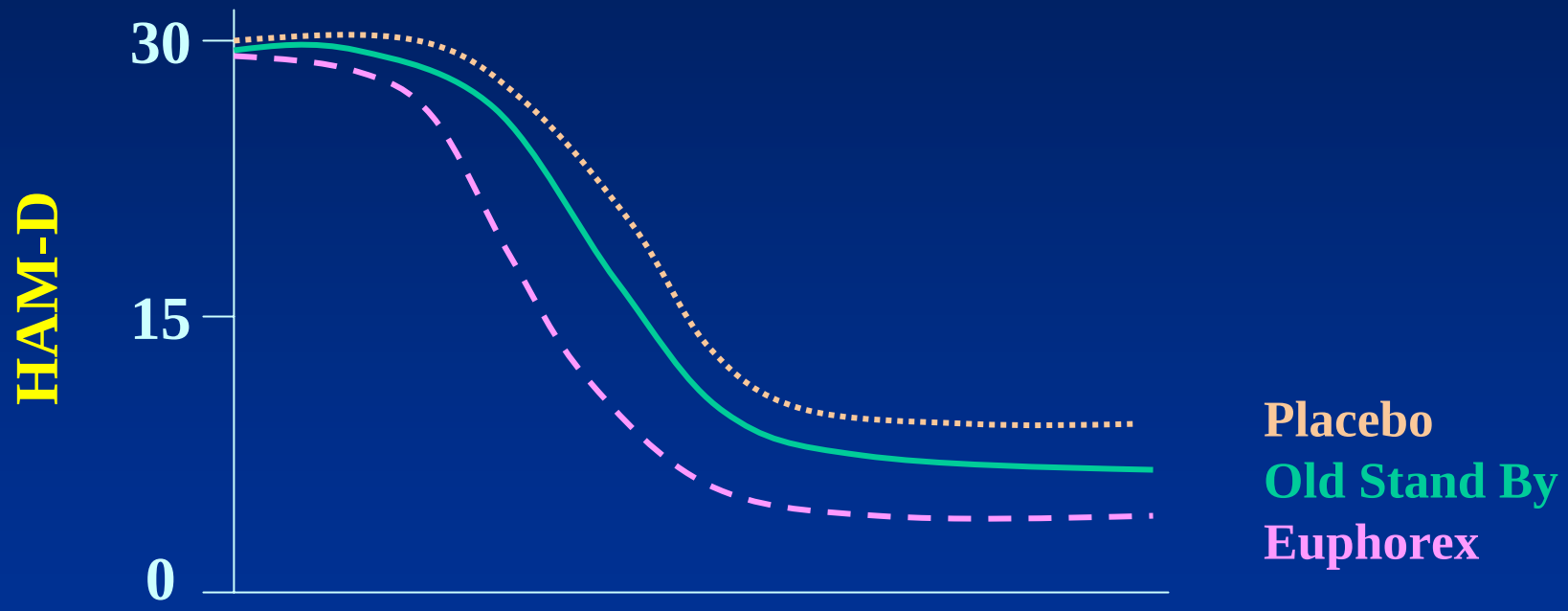
Animal data are usually unreliable

PET data may be more helpful

Do We Need to Use Placebo?

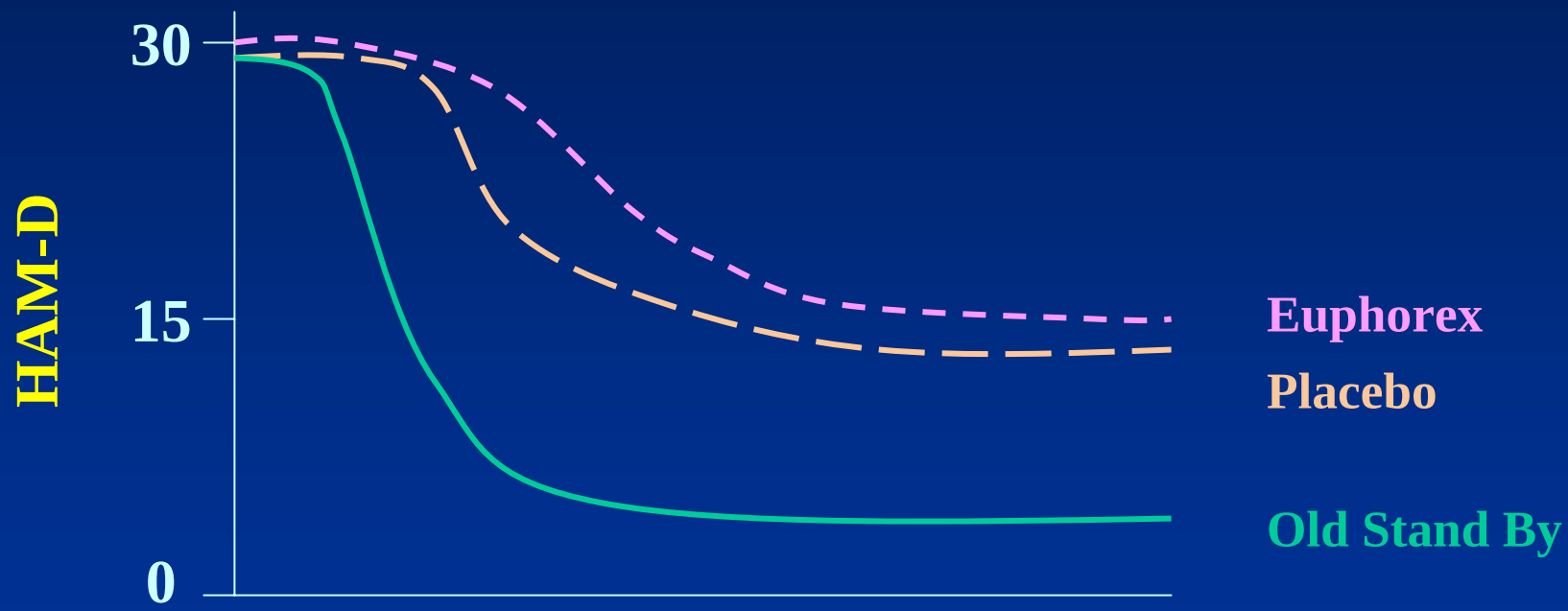


Do We Need to Use Placebo?



Note: This is a failed study

Note: This is a Negative Study



Is Placebo Necessary?

- FDA requirement
- Wide variation in placebo response rates
- No evidence for increased suicide rate in placebo arm
- Concern to prevent inefficacious drugs from reaching the market

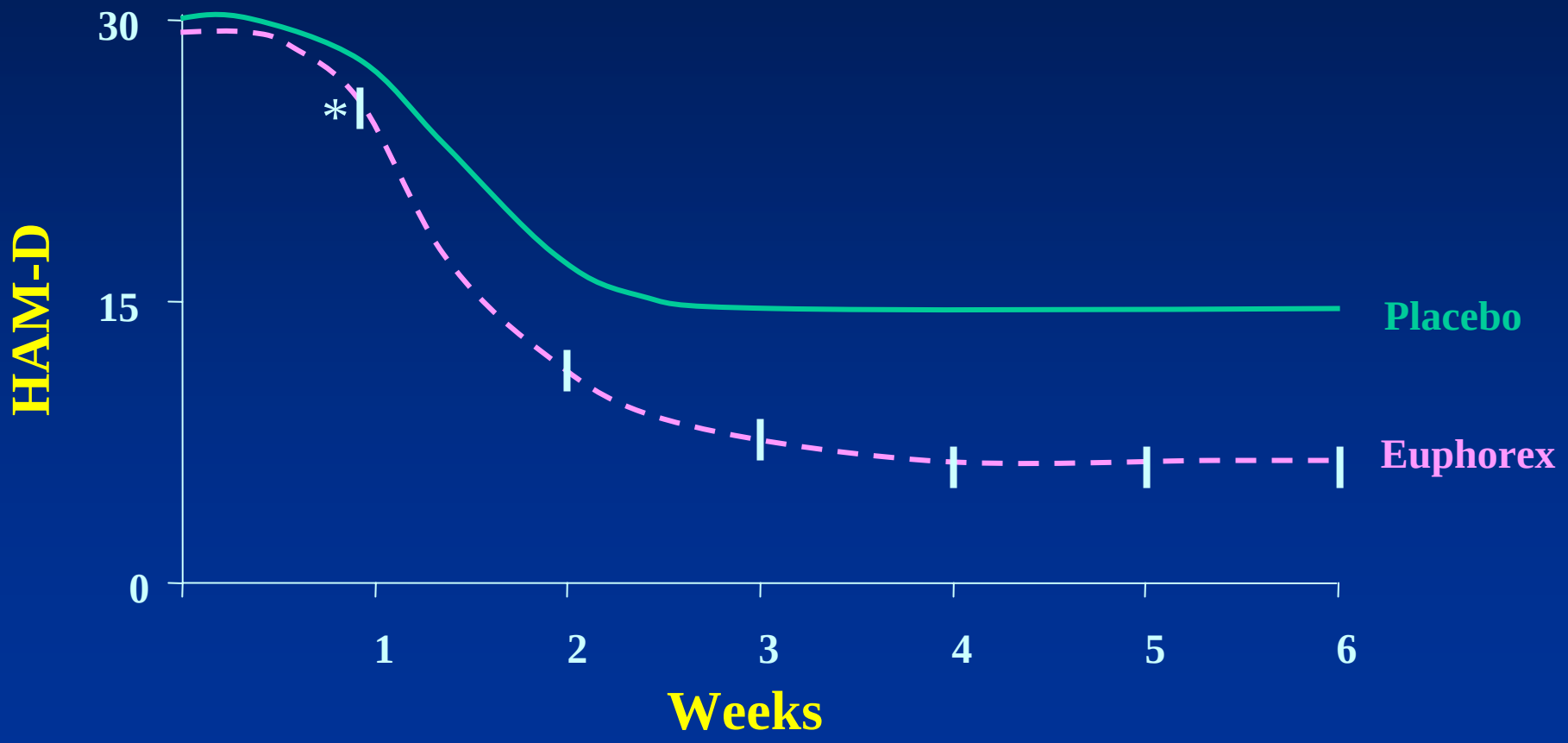
Is the Double-blind Really Maintained?

- The rate of correct guessing is usually better than chance
- If the guess is on the basis of adverse events, the blind is broken
- If the guess is on the basis of perceived efficacy, the blind is maintained

Rating Scales Used in Depression Studies

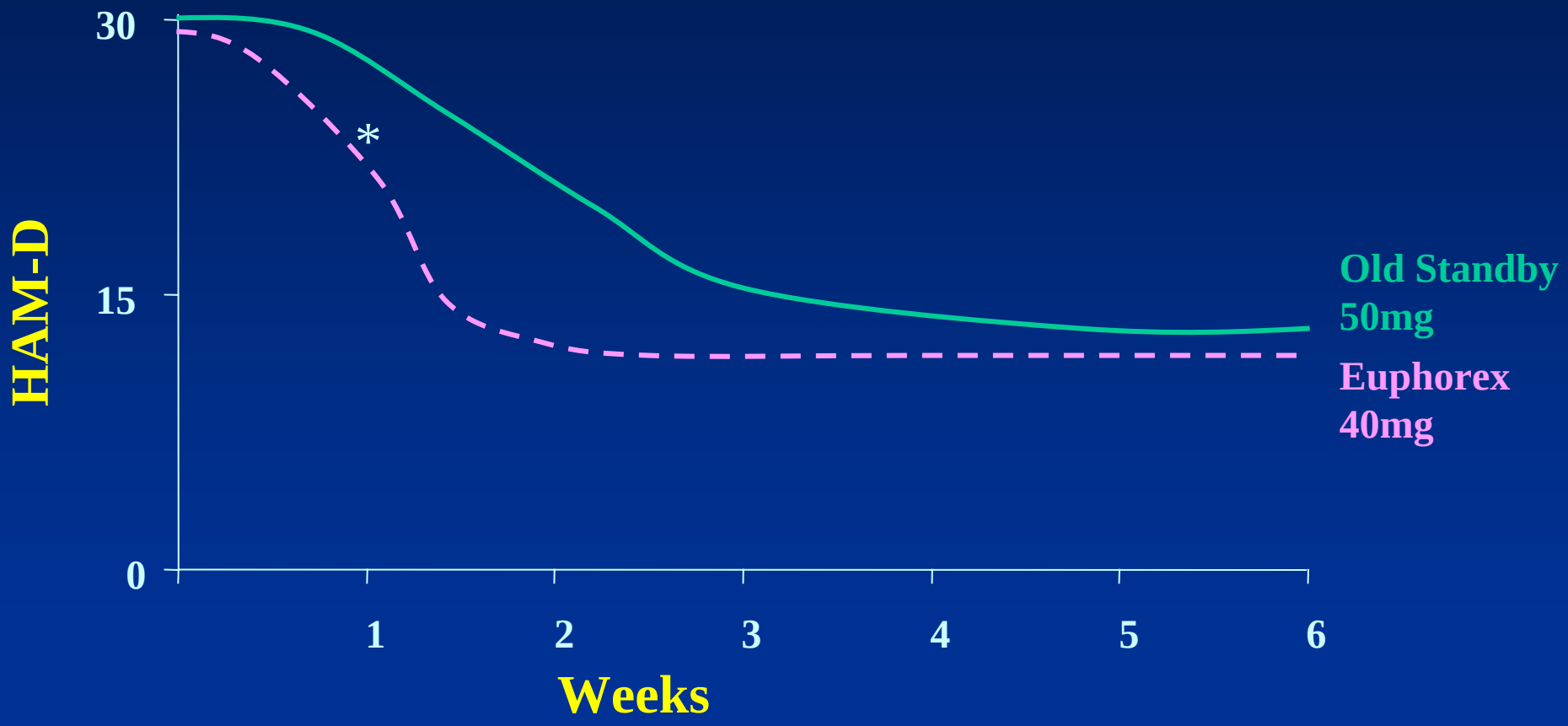
- Hamilton Depression Scale (HAM-D)
- Montgomery-Asbery Depression Scale (MADRS)
- Clincal Global Impression – Severity and Improvement Scales (CGI-S, CGI-I)

Does a New Antidepressant Work Faster than the Others?



* P < 0.05

Does a New Antidepressant Work Faster than the Others?



* P < 0.05

Dose range for Old Standby: 50-300mg
Dose range for Euphorex: 10-40mg

What Does the FDA Require for Approving an NDA?

- Two positive placebo-controlled, Phase III trials
- At least one must usually be done in the United States

Number of Studies Needed to Get Two Positive Studies

- CheerEx 15
- Euphorex 3
- HappyDol 10
- Old Standby 2

Under new regulations, the number of studies needed to get two positive studies must be reported in the label

Problems with Efficacy Studies

- Many exclusion criteria
- Placebo control
- Comorbidities excluded
- Rigid Dosing
- Not “real life”

Are subjects in pharmacological treatment trials of depression representative of patient in routine clinical practice?

- 803 patients evaluated in outpatient practice
- 346 had major depression
- 1/6 would be excluded for bipolar or psychotic depression
- 86% of remaining 293 (252) excluded for comorbid anxiety, substance use, insufficient severity, suicidal ideation

Zimmerman M, Mattia JI, Posternak MA. Am J Psychiatry. 2002;59:469-473

Virtues of Effectiveness Trials

- Minimal exclusion criteria
- Comorbidities allowed
- Clinically determined dosing
- More “real life”

Problems with effectiveness Trials

- What does the drug really treat; depression or comorbidities?
- No controls
- Heterogeneous subject populations

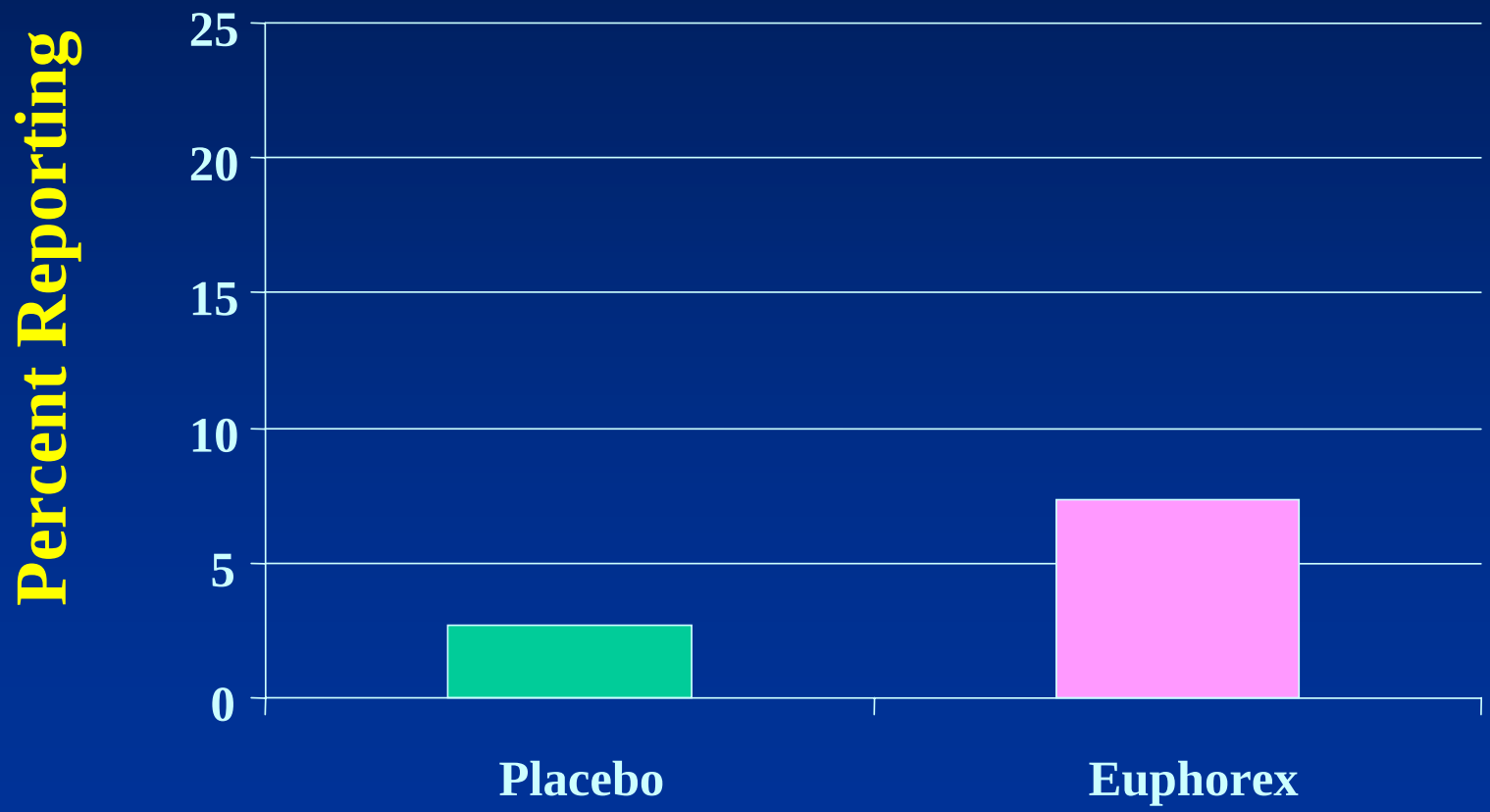
Challenges of Psychotherapy Research

- Cannot have a placebo
- Cannot have a double blind
- Investigator allegiance
- Subject allegiance
- Poor funding sources

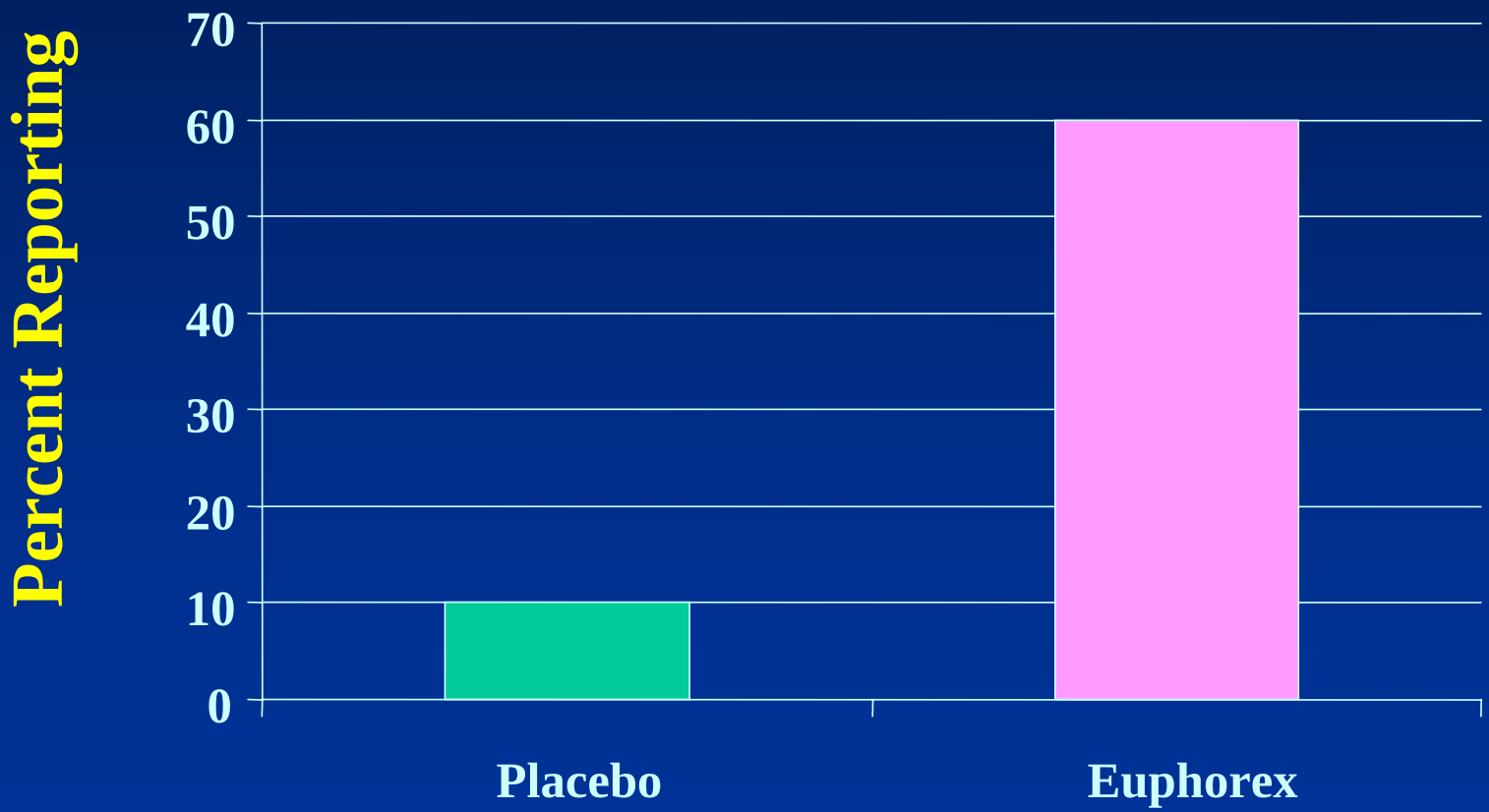
Ways to Reduce Placebo Response

- Placebo “run ins”
- Minimum severity criteria for entry
- Careful training of raters
- Third party baseline assessments
- Careful “incentivising”

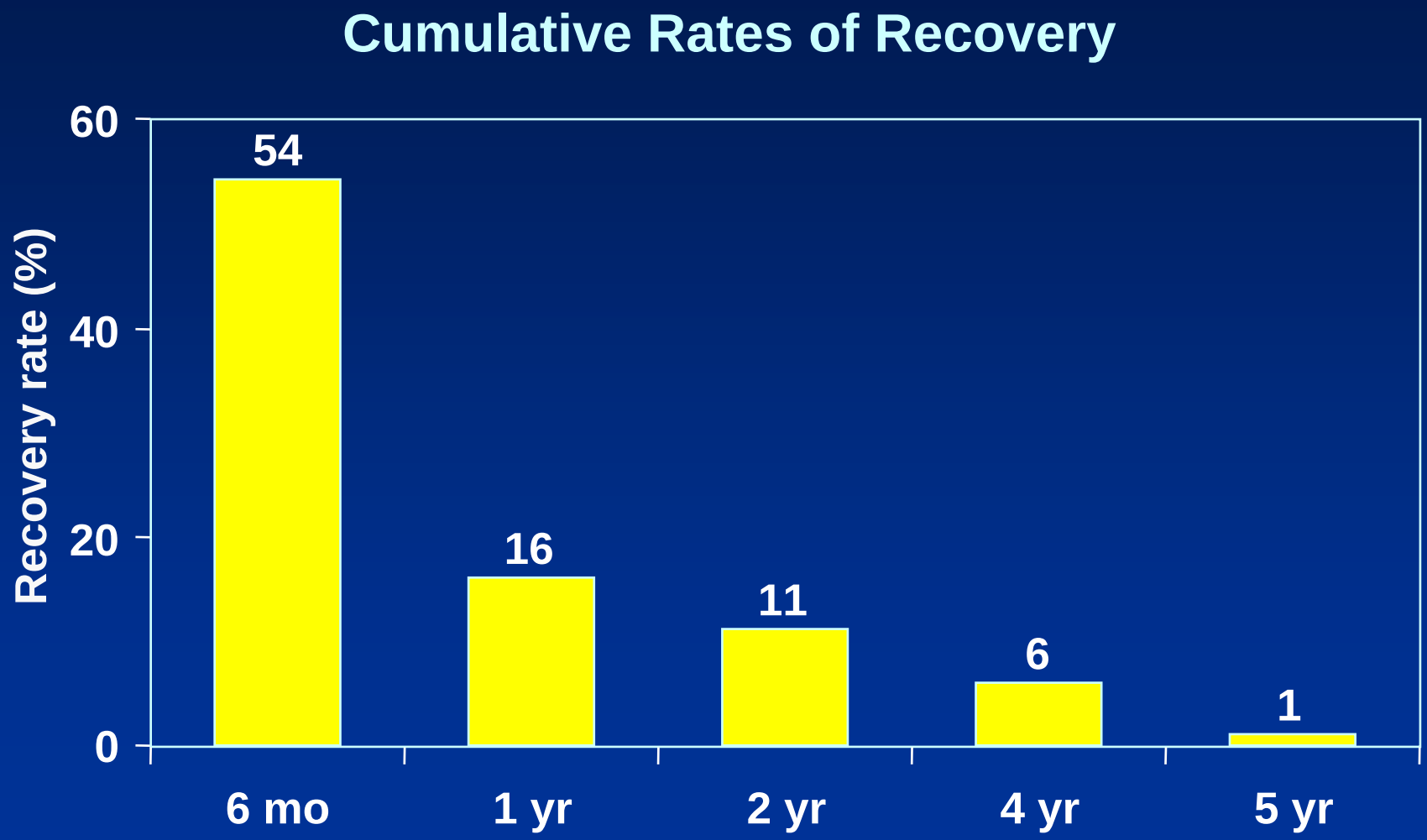
Rate of Sexual Adverse Events by Spontaneous Report



Rate of Sexual Adverse Events by Direct Inquiry



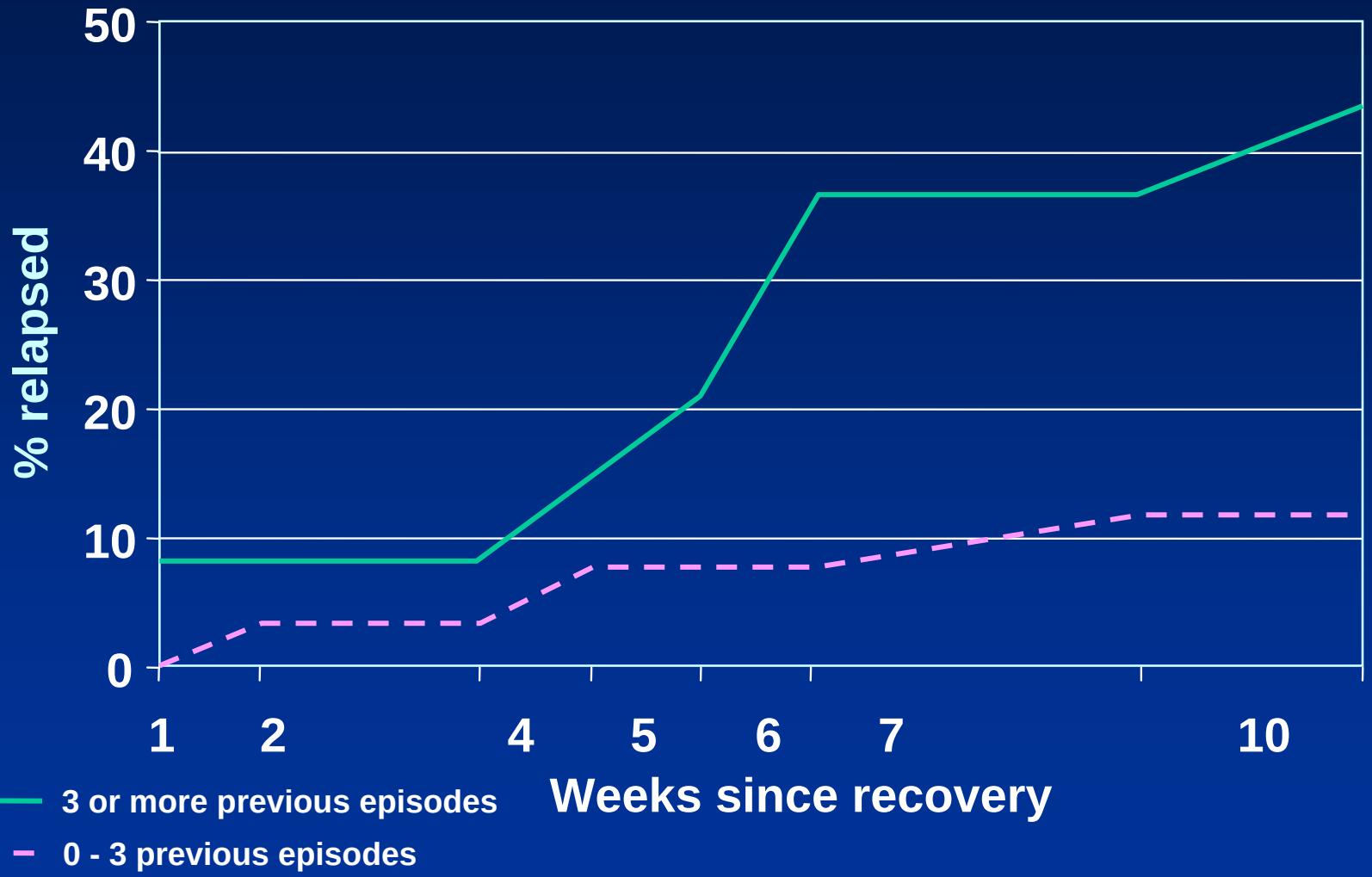
Patients with Major Depression



Keller MB, et al. *Arch Gen Psychiatry*. 1992;49:809-816.

Patients with Major Depression

Cumulative Probability of Relapse



Keller MB, Boland RJ. *Biol Psychiatry*. 1998;44:348-360.

Hypotheses for Low Remission Rates in Major Depression

- Patients satisfied with incomplete response
- Patients, clinicians do not expect remission
- Treatments may not be well tolerated
- Physicians not comfortable or familiar with recommended optimal dosages

Keller MB, et al. *Arch Gen Psychiatry*. 1992;49:809-816.

Response in Major Depression

- Common clinical trial definition
  - ≥ 50% decrease from baseline in HAM-D or MADRS scores
  - Score of 1 or 2 on CGI scale

Thase ME. *J Clin Psychiatry*. 1997;58:393-398.
Cunningham LA. *Ann Clin Psychiatry*. 1997;9:157-164.

Facing the problem: Up to 50% of “responders” do not achieve remission.

Thase ME. *J Clin Psychiatry.* 1999;60(suppl 6):15-19.

Treatment Goal

The goal of treatment with antidepressant medication in the acute phase is the remission of major depressive disorder symptoms

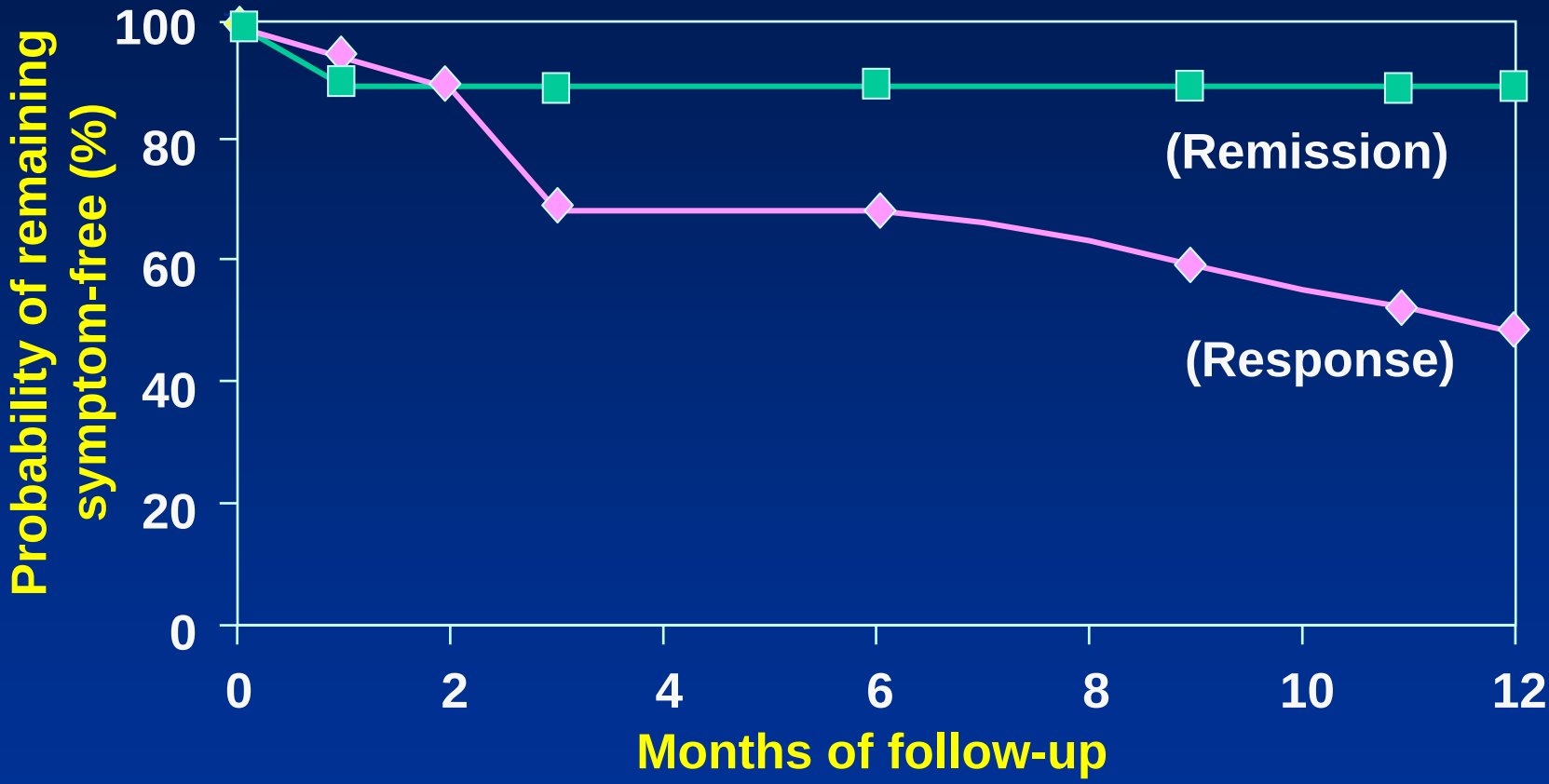
APA Practice Guidelines for the Treatment of Psychiatric Disorders. 2000.

Remission in Major Depression

- HAM-D score ≤ 7
- Patient asymptomatic
  - No longer meets criteria for major depression
  - Minimal or no symptoms
- Psychosocial and occupational functioning restored

Frank E, et al. *Arch Gen Psychiatry*. 1991;48:851-855.
Rush AJ, et al. *Psychiatr Ann*. 1995;25:704.

Incomplete Remission Predicts Greater Relapse*



*After termination of cognitive behavior therapy for depressed patients.

Thase ME, et al. *Am J Psychiatry*. 1992;149:1046-1052.

Characteristics of Pooled Analysis of Venlafaxine vs. SSRIs

- 8 double-blind, randomized trials
  - 7 eight week and 1 six week studies
- 4 placebo-controlled
- 7 outpatient / 1 inpatient
- Sample size (n = 2045)
  - VLX, n = 851
  - SSRI, n = 748
  - PBO, n = 446
- No studies excluded!

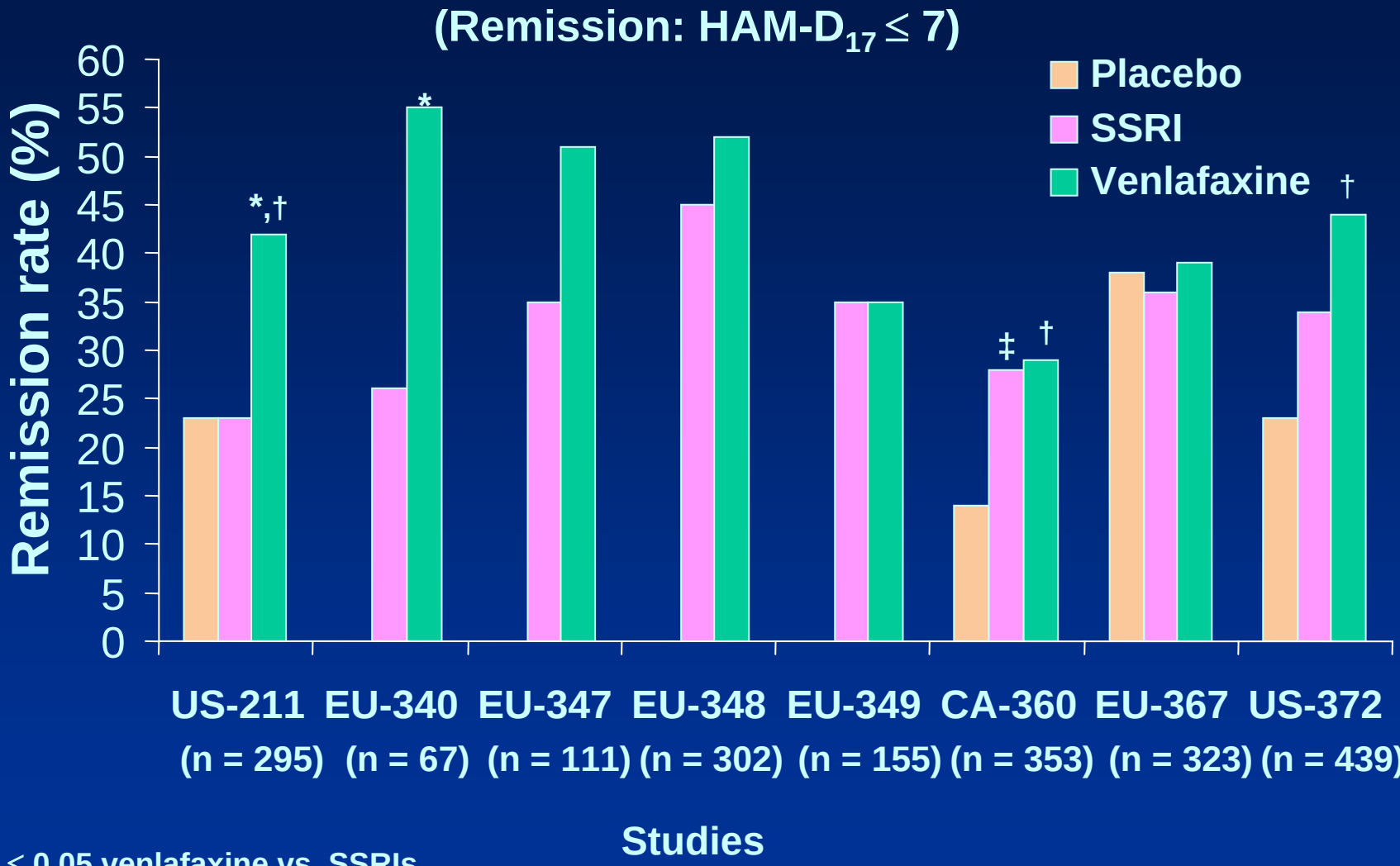
Thase ME, et al. *Br J Psychiatry*. In press.

SSRI Comparators in Meta-Analysis

- Fluoxetine, 5 studies, n = 563
- Paroxetine, 2 studies, n = 160
- Fluvoxamine, 1 study, n = 34

Thase ME, et al. *Br J Psychiatry*. In press.

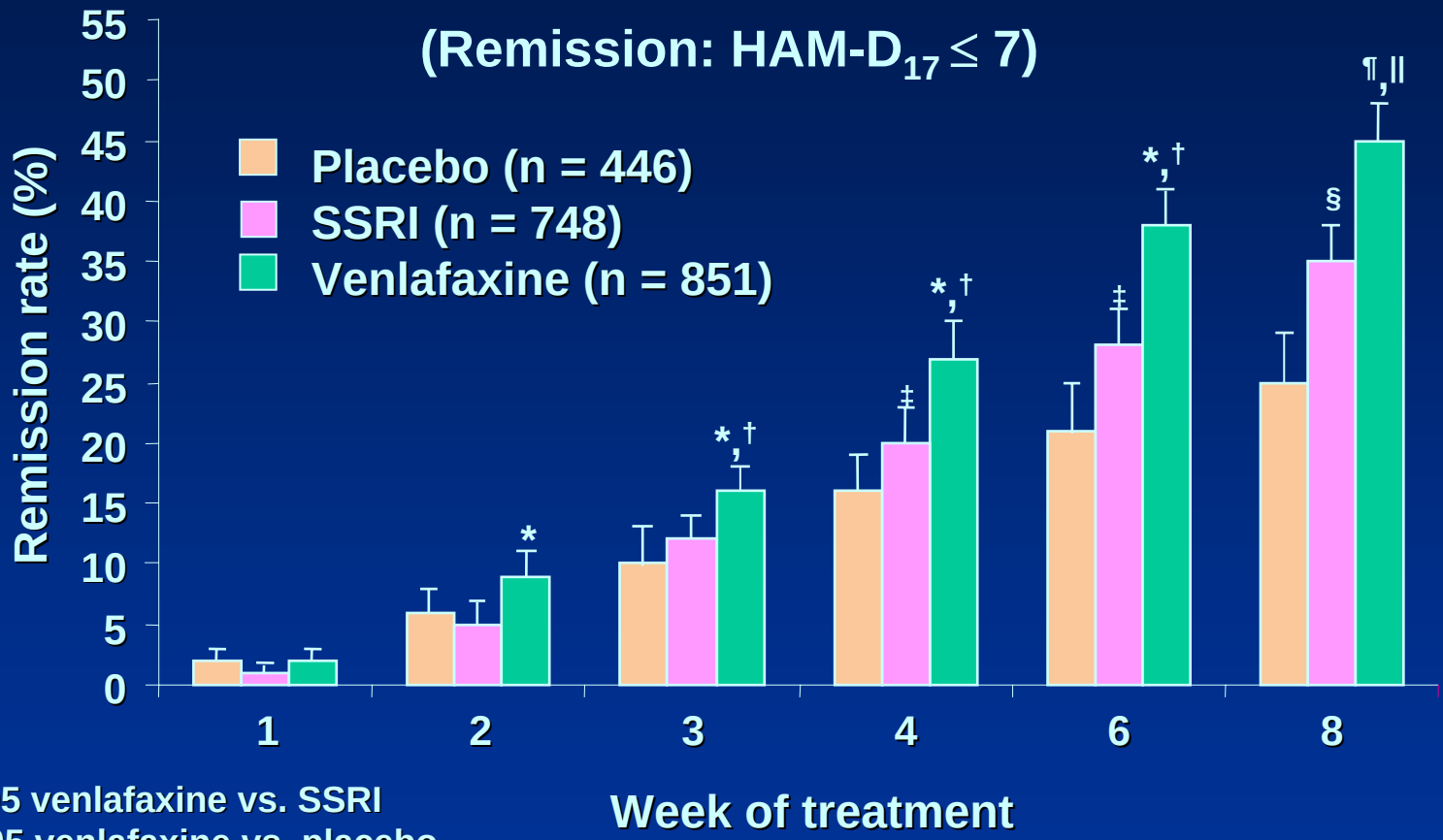
Comparative Studies of Venlafaxine and SSRIs



*$P \leq 0.05$ venlafaxine vs. SSRIs
†$P \leq 0.05$ venlafaxine vs. placebo
‡$P \leq 0.05$ SSRIs vs. placebo

Thase ME, Entsuah R, Rudolph RL. *Br J Psychiatry*. March.2001.

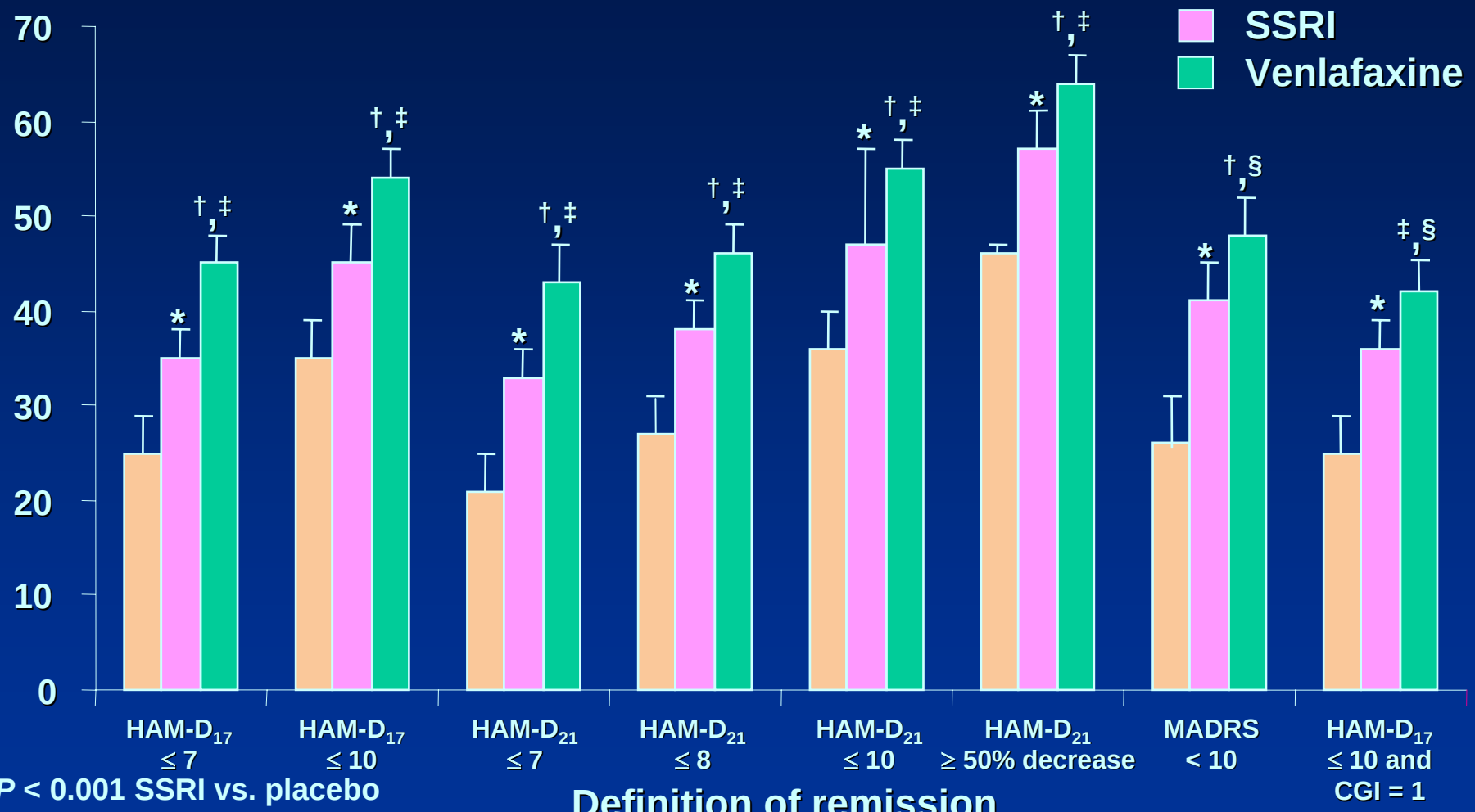
Pooled Analysis of Venlafaxine vs. SSRIs in Depressed Patients



*$P \leq 0.05$ venlafaxine vs. SSRI
†$P \leq 0.05$ venlafaxine vs. placebo
‡$P \leq 0.05$ SSRI vs. placebo
§$P < 0.001$ SSRI vs. placebo
¶$P < 0.001$ venlafaxine vs. SSRI
‖$P < 0.001$ venlafaxine vs. placebo

Thase ME, Entsuah R, Rudolph RL. *Br J Psychiatry*. 2000. In press.

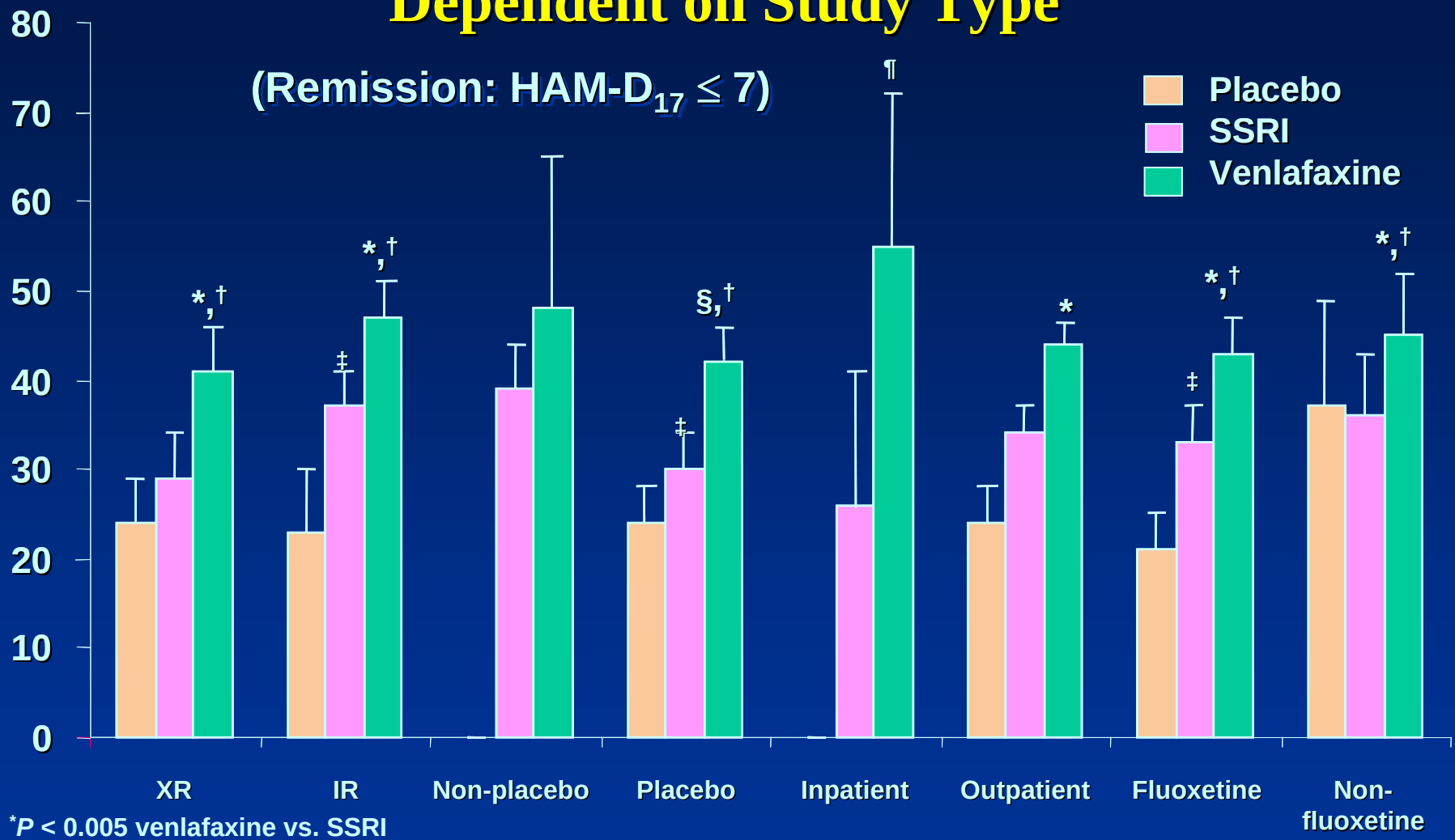
Advantage of Venlafaxine is not Dependent Upon Definition of Remission



*P < 0.001 SSRI vs. placebo
†P < 0.001 venlafaxine vs. SSRI
‡ P < 0.001 venlafaxine vs. placebo
§ P < 0.05 venlafaxine vs. SSRI

Thase ME, Entsuah R, Rudolph RL. *Br J Psychiatry*. 2000. In press.

Advantage of Venlafaxine is not Dependent on Study Type



*P < 0.005 venlafaxine vs. SSRI
†P < 0.001 venlafaxine vs. placebo
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Thase ME, Entsuah R, Rudolph RL. *Br J Psychiatry*. 2000. In press.

Confirmatory Qualitative Review

- 11 other venlafaxine vs. SSRI studies
- More than 2,400 additional patients
- Significant difference in remission in favor of venlafaxine: 12%
- Dose-response relationship

Thase ME, et al. *Br J Psychiatry*. In press.

Remission-Focused Treatment

Summary

- 3 phases: acute, continuation, maintenance
- Choose medication and dose with the greatest probability of
  - Safety in overdose
  - Remission
  - Long-term tolerability
- Measure symptomatic and functional outcomes
- Use acute phase visits to address tactical issues (e.g., dosing, compliance, psychotherapy)
- Obtain symptom resolution in acute treatment

Depression Guideline Panel. AHCPR Publication 93-0550. 1993.